IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lee et al.	Art Unit:	1646
Application No.:	09/485,045	Examiner:	J. Andres
Filed:	May 12, 2000		
Title:	GROWTH DIFFERENTIATION FACTOR-16		

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' BRIEF UNDER 37 CFR 1.192

Sir:

I. INTRODUCTION

This is an appeal from a decision of the Examiner mailed May 19, 2003 (Paper No. 22), rejecting pending claims 2, 4-11, and 53-55 in the above-identified patent application, which is a national phase application of PCT/US98/15148, which claims priority to U.S. Patent Application 60/054,606. Pending claims 2, 4-11, and 53-55 have been finally rejected. The Appeal Brief is being submitted in triplicate (an original and two copies) as required by 37 C.F.R. § 1.192(a).

II. REAL PARTIES IN INTEREST

The subject patent application was filed May 12, 2000, by inventors Se-Jin Lee, Thanh Huynh, and Suzanne Sebald, and assigned Serial No. 09/485,045 ("The Application"). The Application is assigned to The Johns Hopkins School of Medicine ("Appellant"; assignments recorded May 12, 2000, at Reel 010849, Frame 0482).

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on January 20, 2004, in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Karen LePari

Karen LePari

III. RELATED APPEALS AND INTERFERENCES

There is no other appeal or interference that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

IV. STATUS OF THE CLAIMS ON APPEAL

Claims 2, 4 to 11, and 53 to 55 are on appeal.

Claims 1 to 2, 4 to 42, and 53 to 55 are pending. Claims 1, and 12 to 42 have been withdrawn. Claims 3, and 43 to 52 have been cancelled.

The application and claims stand rejected as follows:

Claims 2, 4 to 11, and 53 to 55 stand rejected under 35 U.S.C. § 101, as allegedly lacking a utility.

Claims 2, 4 to 11, and 53 to 55 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement because there is allegedly no utility associated with the claimed polynucleotides.

V. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the final rejection.

Pending claims 2, 4 to 11, and 53 to 55 of the Application, as they stand on Appeal, are attached as Appendix A.

VI. SUMMARY OF THE INVENTION

The present invention provides polynucleotides encoding a growth differentiation factor-16 (GDF-16) polypeptide as set forth in SEQ ID NO:2 (claims 2, 4, 5, and 53). The present invention further provides a polynucleotide that includes a nucleotide sequence according to SEQ ID NO:1, wherein T can also be U; and a nucleotide complementary to the entire nucleotide sequence of SEQ ID NO:1 (claim 53). The present invention further provides expression vectors that contain a polynucleotide encoding a growth differentiation factor-16 (GDF-16) polypeptide

as set forth in SEQ ID NO:2 (claims 4 to 8, and 54), and host cells stably transformed with these vectors (claims 9-11 and 55).

VII. ISSUES

Does the subject matter of the pending claims, as set out above, meet the utility requirement of 35 U.S.C. § 101?

Does the present specification enable a skilled artisan to use the claimed invention as set out above, under 35 U.S.C. 112, first paragraph?

VIII. GROUPING OF CLAIMS

None of the claims rise or fall together.

As discussed in further detail herein, Applicants assert that all of the claimed inventions meet the utility requirement of 35 U.S.C. § 101. However, the claims do not rise and fall together because the utility of the invention is affected by the source of cells from which the claimed polynucleotides are isolated (claims 4 and 5) as well as the specific claimed polynucleotide (compare claims 2 and 53). Furthermore, the utility of the claimed invention can be affected by whether the invention is directed to a polynucleotide (claims 2, 4, 5, and 52), an expression vector (claims 6-8 and 53), or a host cell (claims 9-11 and 54). Therefore, Applicant respectfully asserts that the claims do not rise and fall together.

IX. ARGUMENT

A. Rejection Under 35 U.S.C. § 101

The rejection of claims 2, 4 to 11, and 53 to 55, as being unpatentable under 35 U.S.C. § 101 for allegedly lacking a specific, substantial, and credible utility or a well established utility, is respectfully traversed. To meet the utility requirement, an invention must disclose a utility that is specific, substantial, and credible. MPEP § 2107.2; See also, "Revised Interim Utility Guideline Training Materials" available at http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf. A utility is "specific" if it applies to the claimed subject matter but not to the general class of the

invention. Id. A utility is "substantial" if it defines a real world use. Id. A utility is "credible" if an asserted utility is believable by a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Id. Even if a utility is not explicitly asserted, the utility requirement is met if an invention has a well-established utility (i.e., a person of ordinary skill in the art will immediately appreciate why the invention is useful based on the characteristics of the invention). Courts have clarified that to be useful per 35 U.S.C. § 101 an invention must be capable of some beneficial use in society. Chisum on Patents 4.02; Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278 (D. Del. 1987), aff'd,. 865 F.2d 1247 (Fed. Cir. 1989). A small degree of utility is sufficient to meet the utility requirement. E.I. du Pont De Nemours and Co. v. Berkley and Co., 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980).

It is stated in the Office Action of November 18, 2002 (Paper No. 20) and reiterated in the final Office Action, mailed May 19, 2003 (Paper No. 22), and again in the Advisory Action mailed September 26, 2003 (Paper No. 25) that the claimed subject matter, directed to a polynucleotide encoding a GDF-16 polypeptide, is not supported in the specification by either a specific, substantial, and credible utility or a well-established utility. In particular, it is alleged that no activity or disorder known to be associated with the encoded GDF-16 polypeptide is disclosed, and that further research would be required to identify such an activity or disorder, for example, a disease in which GDF-16 activity could be beneficially affected or which its presence would be diagnostic.

The Final Office Action (Paper No. 22) and Advisory Action (Paper No. 25) maintain that there is no activity known to be associated with the encoded protein and therefore no "real world" use for the polynucleotides of the invention. Regarding the Applicants arguments during prosecution that the utility of the invention of the pending claims is apparent from the disclosure that the polynucleotide of the present invention encodes a TGF-beta family member and the assertion in the specification of utilities associated with this fact and supported by published literature of record in this case (as discussed in further detail below), the Final Office Action and Advisory

Action assert that that the fact that the polynucleotide is a TGF-beta family member does not endow it with a utility.

Applicants respectfully submit that the specification discloses utilities for a GDF-16 protein and encoding polynucleotide, which are substantiated by the published literature. The specification asserts numerous utilities for the invention of the pending claims that are beneficial in society and far exceed "a small degree of utility." Id. The specification discloses that GDF-16 is a TGF-beta family member. Based on this fact and the known activities of various TGF-beta family members, a number of utilities were asserted for GDF-16 encoding polynucleotides, vectors, and host cells that are supported by published literature. For example, the specification discloses that GDF-16 can have cell growth and differentiation activity and can be useful as a marker for a cell proliferative disorder (see page 3, lines 2-4; page 4, lines 1-8). The specification also discloses that a GDF-16 polynucleotide, as well as reagents specific for GDF-16 expression, can be useful for diagnosing and treating a cell proliferative disorder (see, page 19, lines 3-10), for example, a malignant cell proliferative disorder (see page 15, lines 17-24). More specifically, the specification discloses that a GDF-16 polynucleotide can be utilized in detecting and diagnosing a cell proliferative disorder by detecting an altered level of expression compared with that of a normal cell (page 19, lines 3-10). Furthermore, the specification discloses that a GDF-16 polynucleotide can be used to detect a close family member of GDF-16 (page 7, lines 18-23).

Based on this teaching of the specification and published literature that was available at the time of filing of the present invention, at least some of these utilities were well-established. For example, the use of a GDF-16 polynucleotide, as well as reagents specific for GDF-16 expression (e.g. vectors and host cells), for diagnosing a cell proliferative disorder by detecting an altered level of expression compared with that of a normal cell, represents a well-established utility. A number of scientific publications available as of the filing date of the present application, describe specific expression of TGFβ family members, for example the TGFβ-4 (endometrial

bleeding associated factor; "ebaf") gene, in cell proliferative disorders, including endometrial bleeding and adenocarcinoma of the colon, ovaries, and testes (see Kothapalli et al. *J. Clin. Invest.* 99, 2342-2350 (May 15, 1997); and Tabibzadeh et al., *Frontiers in Bioscience* 2, a18-25 (July 15, 1997), both of which are of record in this case). As the Examiner noted in Paper No. 17, the polynucleotide sequence of TGFβ-4 (ebaf), disclosed in U.S. Pat. No. 5,916,751 (The '751 Patent), contains a region of 303 nucleotides that is 92% homologous to SEQ ID NO: 1 of the subject application. As such, Applicants submit that one skilled in the art, viewing the subject application, and having knowledge of the Kothapalli et al. and Tabibzadeh et al. references, would immediately appreciate that the polynucleotides of the invention, and expression vectors and host cells which are useful for the production of the polynucleotides, are useful in the detection of TGFβ family members, such as TGFβ-4 (ebaf), whose expression is correlated with cell proliferative disorders. Therefore, the present invention has a well-established utility.

The Advisory Action alleges that since there is no mention of the relationship of GDF-16 to TGFβ-4 (ebaf) in the present specification or in the art, the use of GDF-16 polynucleotides of the present invention to detect TGFβ-4 (ebaf) cannot represent a well-established utility. As indicated above, the present specification explicitly asserts that GDF-16 polynucleotides, as well as reagents specific for GDF-16 expression, can be useful for diagnosing and treating a cell proliferative disorder and for detecting related family members. It is not necessary that the specification specifically asserts exactly which TGF-beta family members could be detected using polynucleotides of the present invention, because one of ordinary skill in the art will recognize that a routine sequence comparison can be performed to identify TGF-beta family members whose expression is correlated with a cell proliferative disorder that share enough sequence identity with GDF-16 to be identified by polynucleotides of the present invention. Furthermore, the Office Action asserts that since the polynucleotide of the present invention is novel, it cannot have been known in the art to be useful for detection of other TGFβ family members, such as TGFβ-4 (ebaf). However, a person of ordinary skill in the art will recognize

that a polynucleotide does not have to be identical to another polynucleotide to be useful for detecting that polynucleotide.

Regardless of whether or not the present specification explicitly asserts the utility of the present invention to detect a cellular proliferative disorder that involves TGFβ-4 (ebaf), the Utility Guidelines state that a well established utility can be implied if a person of ordinary skill in the art will immediately appreciate why the invention is useful based on the characteristics of the invention. The use of the polynucleotides of the present invention to detect a cellular proliferative disorder would have been apparent to a skilled artisan based on the disclosure of the GDF-16 polynucleotide and polypeptide sequence, and the disclosure that GDF16 is a TGF-beta family member, in view of the relationship of many TGF-beta family members to cell growth and differentiation. This is especially true in view of the disclosure in the published literature, such as the publications mentioned above, that TGF-beta family members with high sequence relatedness to GDF-16, such as TGFβ-4 (ebaf), are specifically expressed in cellular proliferative disorders.

The fact that the present invention had a well-established utility is further supported by the specific examples presented in the Utility Guidelines. Example 12 of The Utility Guidelines indicates in the Caveat section, that a monoclonal antibody has a well-established utility if a receptor bound by the monoclonal antibody is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. This is analogous to the present situation in which the pending claims are directed at polynucleotides that bind a polynucleotide encoding a protein, TGF-beta 4 (ebaf) that is specifically expressed in certain tumors. The Advisory Action indicates that this parallel is "not apt" asserting that unlike an antibody raised against a receptor where there is utility in detecting the receptor, "the disclosed polynucleotide is fortuitously similar to another polynucleotide for which a utility has been disclosed." Applicants respectfully disagree with this assertion. There are many examples in the art where antibodies were raised against receptors for which the antibodies bind to related family members, and for which this

binding to related family members is useful. Furthermore, the polynucleotides of the present invention were not "fortuitously" similar to other TGF-beta family members because they were specifically identified using a TGF-beta family member probe, murine Lefty.

Furthermore, Example 5 of The Utility Guidelines concludes that a claimed invention directed at a partially characterized protein may have a well-established utility, where it is determined that increased levels of protein X are indicative of a disease such as heart disease. This is similar to the present situation in which increased levels of binding of the GDF-16 polynucleotide to ebaf mRNA are indicative of the presence of a tumor. The Advisory Action asserts that this parallel is not appropriate because there is no such utility associated with the identification of GDF-16 as a TGF-beta family member. However, based on the identification of GDF-16 as a TGF-beta family member, one of ordinary skill in the art will recognize that polynucleotides encoding GDF-16 can be used as probes for highly related TGFβ family members, such as TGFβ-4 (ebaf), that are overexpressed in cellular proliferative disorders. Therefore, Applicant respectfully asserts that the parallel with a partially characterized protein having increased levels in heart disease is applicable to the present situation.

Regardless of whether the utilities disclosed in the present application for GDF-16 are well established utilities, they are specific, substantial, and credible utilities. For example, as indicated above, the present specification indicates that because GDF-16 is a TGF-beta family member, it is likely that it can be used to detect a cell proliferative disorder and can be used to detect a close TGF-beta family member. These utilities would not be applicable to all polynucleotides. Therefore, they are specific. Furthermore, they are related to important health issues. Therefore, they are substantial.

The credibility of the asserted utilities for GDF-16 is supported by the published literature. First, there is a plethora of literature available that indicate that various TGF-beta family members have the asserted utilities (See e.g., Kothapalli et al. and Tabibzadeh et al.). Furthermore, based on the Kothapalli et al. and Tabibzadeh et al. references cited above, one skilled in the art viewing the

subject application, reasonably would conclude that a polynucleotide of the present invention encoding GDF-16 can be useful in the detection and diagnosis of a cell proliferative disorder, by using the GDF-16 polynucleotide as a probe for expression of the TGF-beta family member TGFβ-4 (ebaf). Therefore, the published art further establishes the credibility of substantial and specific utilities asserted in the specification for the polynucleotides, vectors, and host cells of the present invention.

In summary, it is respectfully submitted that the polynucleotides, host cells, and expression vectors of the present invention meet the utility requirements of 35 U.S.C. § 101. The present invention provides numerous beneficial uses in society with more than "a small degree of utility," which the courts have stated is sufficient to meet the utility requirement, as cited above. In fact the inventions of the pending claims meet the apparently more stringent criteria set forth in the Utility Guidelines of the USPTO. The claimed inventions have a well-established utility, as well as a specific, substantial, and credibly utility for detecting a cell proliferative disorder, as supported by the specification and the published literature. Accordingly, it is respectfully requested that the rejection of claims 2, 4 to 11 and 53 to 55 under 35 U.S.C. § 101 as allegedly lacking utility, be reversed, and the rejection withdrawn.

B. Rejection Under 35 U.S.C. § 112

The rejection of claims 2, 4 to 11, and 53 to 55, under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure because there is allegedly no utility associated with the claimed polynucleotides, is respectfully traversed. The Advisory Action mailed September 26, 2003 (Paper No. 25) and Final Office Action mailed May 19, 2003 (Paper No. 22) maintain the rejection of the previous Office Action mailed May 30, 2002 (Paper No. 17) that the rejected claims are not enabled because there is allegedly no utility associated with the claimed polynucleotides.

As indicated above, Applicants respectfully assert that the polynucleotides, expression vectors, and host cells of the pending claims had a utility as of the filing date of the present application, of

being useful in detecting cellular proliferative disorders, such as by detecting related TGF-beta family members. This utility is asserted in the present specification and supported by the published literature. The specification discloses that GDF-16 is a TGF-beta family member. Based on this fact and the known activities of various TGF-beta family members, a number of utilities were asserted for GDF-16 encoding polynucleotides, vectors, and host cells that are supported by published literature. For example, the specification discloses that GDF-16 can have cell growth and differentiation activity and can be useful as a marker for a cell proliferative disorder (see page 3, lines 2-4; page 4, lines 1-8). The specification also discloses that a GDF-16 polynucleotide, as well as reagents specific for GDF-16 expression, can be useful for diagnosing and treating a cell proliferative disorder (see, page 19, lines 3-10), for example, a malignant cell proliferative disorder (see page 15, lines 17-24). More specifically, the specification discloses that a GDF-16 polynucleotide can be utilized in detecting and diagnosing a cell proliferative disorder by detecting an altered level of expression compared with that of a normal cell (page 19, lines 3-10). Furthermore, the specification discloses that a GDF-16 polynucleotide can be used to detect a close family member of GDF-16 (page 7, lines 18-23).

As indicated above, a number of scientific publications available as of the filing date of the present application, describe specific expression of TGFβ family members, for example the TGFβ-4 (endometrial bleeding associated factor; "ebaf") gene, in cell proliferative disorders, including endometrial bleeding and adenocarcinoma of the colon, ovaries, and testes (see Kothapalli et al. *J. Clin. Invest.* 99, 2342-2350 (May 15, 1997); and Tabibzadeh et al., *Frontiers in Bioscience* 2, a18-25 (July 15, 1997), both of which are of record in this case). As the Examiner noted in Paper No. 17, the polynucleotide sequence of TGFβ-4 (ebaf), disclosed in U.S. Pat. No. 5,916,751 (The '751 Patent), contains a region of 303 nucleotides that is 92% homologous to SEQ ID NO: 1 of the subject application. As such, Applicants submit that one skilled in the art, viewing the subject application, and having knowledge of the Kothapalli et al. and Tabibzadeh et al. references, would appreciate that the polynucleotides of the invention, and expression vectors and host cells which are useful for the production of the polynucleotides, are

useful in the detection of TGFβ family members whose expression is correlated with cell proliferative disorders, such as TGFβ-4 (ebaf). Therefore, the utilities taught in the specification are further supported by the published literature. Accordingly, it is respectfully requested that the rejection of claims 2, 4 to 11, and 53 to 55, under 35 U.S.C. § 112, first paragraph, be reversed, and the rejection withdrawn.

APPENDICES

Appendix A contains a copy of pending claims 1 to 2, 4 to 42, and 53 to 55. Claims 2, 4 to 11, and 53 to 55 are on appeal. Claims 1, and 12 to 42 have been withdrawn. Claims 3, and 43 to 52 have been cancelled.

CONCLUSION

In view of the above remarks, it is respectfully submitted that claims 2, 4 to 11, and 53 to 55 are in condition for allowance. Accordingly, it is respectfully submitted that the decision of the Examiner, rejecting claims 2, 4 to 11, and 53 to 55, under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 101, be reversed, and the rejections withdrawn.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: January 20, 2004

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EXHIBIT A

CLAIMS PENDING ON APPEAL

1. (Withdrawn): Substantially pure growth differentiation factor-16 (GDF-16).

2. (Previously Presented): An isolated polynucleotide sequence encoding the growth differentiation factor-16 (GDF-16) polypeptide as set forth in SEQ ID NO: 2.

3. (Canceled)

4. (Previously Presented): The polynucleotide sequence of claim 2, wherein the polynucleotide is isolated from a mammalian cell.

5. (Previously Presented): The polynucleotide of claim 4, wherein the mammalian cell is selected from the group consisting of mouse, rat, and human cell.

6. (Previously Presented): An expression vector including the polynucleotide of claim 2.

7. (Previously Presented): The vector of claim 6, wherein the vector is a plasmid.

8. (Previously Presented): The vector of claim 6, wherein the vector is a virus.

9. (Previously Presented): A host cell stably transformed with the vector of claim 6.

10. (Previously Presented): The host cell of claim 9, wherein the cell is prokaryotic.

11. (Previously Presented): The host cell of claim 9, wherein the cell is eukaryotic.

12. (Withdrawn): Antibodies that bind to the polypeptide of claim 1 or fragments thereof.

13. (Withdrawn): The antibodies of claim 12, wherein the antibodies are polyclonal

14. (Withdrawn): The antibodies of claim 12, wherein the antibodies are monoclonal.

15. (Withdrawn): A method of detecting a cell proliferative disorder comprising contacting the antibody of claim 12 with a specimen of a subject suspected of having a GDF-16 associated disorder and detecting binding of the antibody.

16. (Withdrawn): The method of claim 15, wherein the detecting is in vivo.

17. (Withdrawn): The method of claim 16, wherein the antibody is detectably labeled.

18. (Withdrawn): The method of claim 17, wherein the detectable label is selected from the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound and a chemiluminescent compound.

19. (Withdrawn): The method of claim 15, wherein the detection is in vitro.

20. (Withdrawn): The method of claim 19, wherein the antibody is detectably labeled.

21. (Withdrawn): The method of claim 20, wherein the label is selected from- the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound, a chemoluminescent compound and an enzyme.

22. (Withdrawn): A method of treating a cell proliferative disorder or immunologic disorder associated with expression of GDF-16, comprising contacting the cells with a reagent which suppresses the GDF-16 activity.

23. (Withdrawn): The method of claim 22, wherein the reagent is an anti-GDF- 16 antibody.

24. (Withdrawn): The method of claim 22, wherein the reagent is a GDF-16 antisense sequence.

25. (Withdrawn): The method of claim 22, wherein the reagent which suppresses GDF-16 activity is introduced to a cell using a vector.

26. (Withdrawn): The method of claim 25, wherein the vector is a colloidal dispersion system.

27. (Withdrawn): The method of claim 26, wherein the colloidal dispersion system is a liposome.

28. (Withdrawn): The method of claim 27, wherein the liposome is essentially target specific.

29. (Withdrawn): The method of claim 28, wherein the liposome is anatomically targeted.

30. (Withdrawn): The method of claim 29, wherein the liposome is mechanistically targeted.

31. (Withdrawn): The method of claim 30, wherein the mechanistic targeting is passive.

32. (Withdrawn): The method of claim 30, wherein the mechanistic targeting is active.

33. (Withdrawn): The method of claim 32, wherein the liposome is actively targeted by coupling with a moiety selected from the group consisting of a sugar, a glycolipid, and a protein.

34. (Withdrawn): The method of claim 33, wherein the protein moiety is an antibody.

35. (Withdrawn): The method of claim 34, wherein the vector is a virus.

36. (Withdrawn): The method of claim 35, wherein the virus is an RNA virus.

37. (Withdrawn): The method of claim 36, wherein the RNA virus is a retrovirus.

38. (Withdrawn): The method of claim 37, wherein the retrovirus is essentially target specific.

39. (Withdrawn): The method of claim 38, wherein a moiety for target specificity is encoded by a polynucleotide inserted into the retroviral genome.

40. (Withdrawn): The method of claim 38, wherein a moiety for target specificity is selected from the group consisting of a sugar, a glycolipid. and a protein.

41. (Withdrawn): The method of claim 40, wherein the protein is an antibody.

42. (Withdrawn): A method for identifying a GDF-16 receptor polypeptide comprising:

a) incubating components comprising GDF- 16 polypeptide and a cell expressing a receptor or a soluble receptor under conditions sufficient to allow the GDF-16 to bind to the receptor;

b) measuring the binding of the GDF-16 polypeptide to the receptor; and

c) isolating the receptor.

43-52 (Canceled).

53. (Previously Presented): An isolated polynucleotide comprising:

a) a nucleotide sequence encoding the growth differentiation factor-16 (GDF-16) polypeptide as set forth in SEQ ID NO: 2;

b) a nucleotide sequence according to SEQ ID NO:1, wherein T can also be U; or

c) a nucleotide sequence complementary to the entire nucleotide sequence of SEQ ID NO:1.

54. (Previously Presented): An expression vector including the polynucleotide of claim 53.

55. (Previously Presented): A host cell stably transformed with the vector of claim 54.

PATENT
Attorney Docket No.: JHU1440-1

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II. REAL PARTIES IN INTEREST

The subject patent application was filed May 12, 2000, by inventors Se-Jin Lee, Thanh Huynh, and Suzanne Sebald, and assigned Serial No. 09/485,045 ("The Application"). The Application is assigned to The Johns Hopkins School of Medicine ("Appellant"; assignments recorded May 12, 2000, at Reel 010849, Frame 0482).

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on January 20, 2004, in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Karen LePari

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Gray Cary\GT\6379388.2
104659-159642

III. RELATED APPEALS AND INTERFERENCES

There is no other appeal or interference that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

IV. STATUS OF THE CLAIMS ON APPEAL

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VI. SUMMARY OF THE INVENTION

The present invention provides polynucleotides encoding a growth differentiation factor-16 (GDF-16) polypeptide as set forth in SEQ ID NO:2 (claims 2, 4, 5, and 53). The present invention further provides a polynucleotide that includes a nucleotide sequence according to SEQ ID NO:1, wherein T can also be U; and a nucleotide complementary to the entire nucleotide sequence of SEQ ID NO:1 (claim 53). The present invention further provides expression vectors that contain a polynucleotide encoding a growth differentiation factor-16 (GDF-16) polypeptide

as set forth in SEQ ID NO:2 (claims 4 to 8, and 54), and host cells stably transformed with these vectors (claims 9-11 and 55).

VII. ISSUES

Does the subject matter of the pending claims, as set out above, meet the utility requirement of 35 U.S.C. § 101?

Does the present specification enable a skilled artisan to use the claimed invention as set out above, under 35 U.S.C. 112, first paragraph?

VIII. GROUPING OF CLAIMS

None of the claims rise or fall together.

As discussed in further detail herein, Applicants assert that all of the claimed inventions meet the utility requirement of 35 U.S.C. § 101. However, the claims do not rise and fall together because the utility of the invention is affected by the source of cells from which the claimed polynucleotides are isolated (claims 4 and 5) as well as the specific claimed polynucleotide (compare claims 2 and 53). Furthermore, the utility of the claimed invention can be affected by whether the invention is directed to a polynucleotide (claims 2, 4, 5, and 52), an expression vector (claims 6-8 and 53), or a host cell (claims 9-11 and 54). Therefore, Applicant respectfully asserts that the claims do not rise and fall together.

IX. ARGUMENT

A. Rejection Under 35 U.S.C. § 101

The rejection of claims 2, 4 to 11, and 53 to 55, as being unpatentable under 35 U.S.C. § 101 for allegedly lacking a specific, substantial, and credible utility or a well established utility, is respectfully traversed. To meet the utility requirement, an invention must disclose a utility that is specific, substantial, and credible. MPEP § 2107.2; See also, "Revised Interim Utility Guideline Training Materials" available at http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf. A utility is "specific" if it applies to the claimed subject matter but not to the general class of the

invention. Id. A utility is "substantial" if it defines a real world use. Id. A utility is "credible" if an asserted utility is believable by a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Id. Even if a utility is not explicitly asserted, the utility requirement is met if an invention has a well-established utility (i.e., a person of ordinary skill in the art will immediately appreciate why the invention is useful based on the characteristics of the invention). Courts have clarified that to be useful per 35 U.S.C. § 101 an invention must be capable of some beneficial use in society. Chisum on Patents 4.02; Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278 (D. Del. 1987), aff'd,. 865 F.2d 1247 (Fed. Cir. 1989). A small degree of utility is sufficient to meet the utility requirement. E.I. du Pont De Nemours and Co. v. Berkley and Co., 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980).

It is stated in the Office Action of November 18, 2002 (Paper No. 20) and reiterated in the final Office Action, mailed May 19, 2003 (Paper No. 22), and again in the Advisory Action mailed September 26, 2003 (Paper No. 25) that the claimed subject matter, directed to a polynucleotide encoding a GDF-16 polypeptide, is not supported in the specification by either a specific, substantial, and credible utility or a well-established utility. In particular, it is alleged that no activity or disorder known to be associated with the encoded GDF-16 polypeptide is disclosed, and that further research would be required to identify such an activity or disorder, for example, a disease in which GDF-16 activity could be beneficially affected or which its presence would be diagnostic.

The Final Office Action (Paper No. 22) and Advisory Action (Paper No. 25) maintain that there is no activity known to be associated with the encoded protein and therefore no "real world" use for the polynucleotides of the invention. Regarding the Applicants arguments during prosecution that the utility of the invention of the pending claims is apparent from the disclosure that the polynucleotide of the present invention encodes a TGF-beta family member and the assertion in the specification of utilities associated with this fact and supported by published literature of record in this case (as discussed in further detail below), the Final Office Action and Advisory

Action assert that that the fact that the polynucleotide is a TGF-beta family member does not endow it with a utility.

Applicants respectfully submit that the specification discloses utilities for a GDF-16 protein and encoding polynucleotide, which are substantiated by the published literature. The specification asserts numerous utilities for the invention of the pending claims that are beneficial in society and far exceed "a small degree of utility." Id. The specification discloses that GDF-16 is a TGF-beta family member. Based on this fact and the known activities of various TGF-beta family members, a number of utilities were asserted for GDF-16 encoding polynucleotides, vectors, and host cells that are supported by published literature. For example, the specification discloses that GDF-16 can have cell growth and differentiation activity and can be useful as a marker for a cell proliferative disorder (see page 3, lines 2-4; page 4, lines 1-8). The specification also discloses that a GDF-16 polynucleotide, as well as reagents specific for GDF-16 expression, can be useful for diagnosing and treating a cell proliferative disorder (see, page 19, lines 3-10), for example, a malignant cell proliferative disorder (see page 15, lines 17-24). More specifically, the specification discloses that a GDF-16 polynucleotide can be utilized in detecting and diagnosing a cell proliferative disorder by detecting an altered level of expression compared with that of a normal cell (page 19, lines 3-10). Furthermore, the specification discloses that a GDF-16 polynucleotide can be used to detect a close family member of GDF-16 (page 7, lines 18-23).

Based on this teaching of the specification and published literature that was available at the time of filing of the present invention, at least some of these utilities were well-established. For example, the use of a GDF-16 polynucleotide, as well as reagents specific for GDF-16 expression (e.g. vectors and host cells), for diagnosing a cell proliferative disorder by detecting an altered level of expression compared with that of a normal cell, represents a well-established utility. A number of scientific publications available as of the filing date of the present application, describe specific expression of TGFβ family members, for example the TGFβ-4 (endometrial

bleeding associated factor; "ebaf") gene, in cell proliferative disorders, including endometrial bleeding and adenocarcinoma of the colon, ovaries, and testes (see Kothapalli et al. *J. Clin. Invest.* 99, 2342-2350 (May 15, 1997); and Tabibzadeh et al., *Frontiers in Bioscience* 2, a18-25 (July 15, 1997), both of which are of record in this case). As the Examiner noted in Paper No. 17, the polynucleotide sequence of TGFβ-4 (ebaf), disclosed in U.S. Pat. No. 5,916,751 (The '751 Patent), contains a region of 303 nucleotides that is 92% homologous to SEQ ID NO: 1 of the subject application. As such, Applicants submit that one skilled in the art, viewing the subject application, and having knowledge of the Kothapalli et al. and Tabibzadeh et al. references, would immediately appreciate that the polynucleotides of the invention, and expression vectors and host cells which are useful for the production of the polynucleotides, are useful in the detection of TGFβ family members, such as TGFβ-4 (ebaf), whose expression is correlated with cell proliferative disorders. Therefore, the present invention has a well-established utility.

The Advisory Action alleges that since there is no mention of the relationship of GDF-16 to TGFβ-4 (ebaf) in the present specification or in the art, the use of GDF-16 polynucleotides of the present invention to detect TGFβ-4 (ebaf) cannot represent a well-established utility. As indicated above, the present specification explicitly asserts that GDF-16 polynucleotides, as well as reagents specific for GDF-16 expression, can be useful for diagnosing and treating a cell proliferative disorder and for detecting related family members. It is not necessary that the specification specifically asserts exactly which TGF-beta family members could be detected using polynucleotides of the present invention, because one of ordinary skill in the art will recognize that a routine sequence comparison can be performed to identify TGF-beta family members whose expression is correlated with a cell proliferative disorder that share enough sequence identity with GDF-16 to be identified by polynucleotides of the present invention. Furthermore, the Office Action asserts that since the polynucleotide of the present invention is novel, it cannot have been known in the art to be useful for detection of other TGFβ family members, such as TGFβ-4 (ebaf). However, a person of ordinary skill in the art will recognize

that a polynucleotide does not have to be identical to another polynucleotide to be useful for detecting that polynucleotide.

Regardless of whether or not the present specification explicitly asserts the utility of the present invention to detect a cellular proliferative disorder that involves TGFβ-4 (ebaf), the Utility Guidelines state that a well established utility can be implied if a person of ordinary skill in the art will immediately appreciate why the invention is useful based on the characteristics of the invention. The use of the polynucleotides of the present invention to detect a cellular proliferative disorder would have been apparent to a skilled artisan based on the disclosure of the GDF-16 polynucleotide and polypeptide sequence, and the disclosure that GDF16 is a TGF-beta family member, in view of the relationship of many TGF-beta family members to cell growth and differentiation. This is especially true in view of the disclosure in the published literature, such as the publications mentioned above, that TGF-beta family members with high sequence relatedness to GDF-16, such as TGFβ-4 (ebaf), are specifically expressed in cellular proliferative disorders.

The fact that the present invention had a well-established utility is further supported by the specific examples presented in the Utility Guidelines. Example 12 of The Utility Guidelines indicates in the Caveat section, that a monoclonal antibody has a well-established utility if a receptor bound by the monoclonal antibody is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. This is analogous to the present situation in which the pending claims are directed at polynucleotides that bind a polynucleotide encoding a protein, TGF-beta 4 (ebaf) that is specifically expressed in certain tumors. The Advisory Action indicates that this parallel is "not apt" asserting that unlike an antibody raised against a receptor where there is utility in detecting the receptor, "the disclosed polynucleotide is fortuitously similar to another polynucleotide for which a utility has been disclosed." Applicants respectfully disagree with this assertion. There are many examples in the art where antibodies were raised against receptors for which the antibodies bind to related family members, and for which this

binding to related family members is useful. Furthermore, the polynucleotides of the present invention were not "fortuitously" similar to other TGF-beta family members because they were specifically identified using a TGF-beta family member probe, murine Lefty.

Furthermore, Example 5 of The Utility Guidelines concludes that a claimed invention directed at a partially characterized protein may have a well-established utility, where it is determined that increased levels of protein X are indicative of a disease such as heart disease. This is similar to the present situation in which increased levels of binding of the GDF-16 polynucleotide to ebaf mRNA are indicative of the presence of a tumor. The Advisory Action asserts that this parallel is not appropriate because there is no such utility associated with the identification of GDF-16 as a TGF-beta family member. However, based on the identification of GDF-16 as a TGF-beta family member, one of ordinary skill in the art will recognize that polynucleotides encoding GDF-16 can be used as probes for highly related TGFβ family members, such as TGFβ-4 (ebaf), that are overexpressed in cellular proliferative disorders. Therefore, Applicant respectfully asserts that the parallel with a partially characterized protein having increased levels in heart disease is applicable to the present situation.

Regardless of whether the utilities disclosed in the present application for GDF-16 are well established utilities, they are specific, substantial, and credible utilities. For example, as indicated above, the present specification indicates that because GDF-16 is a TGF-beta family member, it is likely that it can be used to detect a cell proliferative disorder and can be used to detect a close TGF-beta family member. These utilities would not be applicable to all polynucleotides. Therefore, they are specific. Furthermore, they are related to important health issues. Therefore, they are substantial.

The credibility of the asserted utilities for GDF-16 is supported by the published literature. First, there is a plethora of literature available that indicate that various TGF-beta family members have the asserted utilities (See e.g., Kothapalli et al. and Tabibzadeh et al.). Furthermore, based on the Kothapalli et al. and Tabibzadeh et al. references cited above, one skilled in the art viewing the

subject application, reasonably would conclude that a polynucleotide of the present invention encoding GDF-16 can be useful in the detection and diagnosis of a cell proliferative disorder, by using the GDF-16 polynucleotide as a probe for expression of the TGF-beta family member TGFβ-4 (ebaf). Therefore, the published art further establishes the credibility of substantial and specific utilities asserted in the specification for the polynucleotides, vectors, and host cells of the present invention.

In summary, it is respectfully submitted that the polynucleotides, host cells, and expression vectors of the present invention meet the utility requirements of 35 U.S.C. § 101. The present invention provides numerous beneficial uses in society with more than "a small degree of utility," which the courts have stated is sufficient to meet the utility requirement, as cited above. In fact the inventions of the pending claims meet the apparently more stringent criteria set forth in the Utility Guidelines of the USPTO. The claimed inventions have a well-established utility, as well as a specific, substantial, and credibly utility for detecting a cell proliferative disorder, as supported by the specification and the published literature. Accordingly, it is respectfully requested that the rejection of claims 2, 4 to 11 and 53 to 55 under 35 U.S.C. § 101 as allegedly lacking utility, be reversed, and the rejection withdrawn.

B. Rejection Under 35 U.S.C. § 112

The rejection of claims 2, 4 to 11, and 53 to 55, under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure because there is allegedly no utility associated with the claimed polynucleotides, is respectfully traversed. The Advisory Action mailed September 26, 2003 (Paper No. 25) and Final Office Action mailed May 19, 2003 (Paper No. 22) maintain the rejection of the previous Office Action mailed May 30, 2002 (Paper No. 17) that the rejected claims are not enabled because there is allegedly no utility associated with the claimed polynucleotides.

As indicated above, Applicants respectfully assert that the polynucleotides, expression vectors, and host cells of the pending claims had a utility as of the filing date of the present application, of

being useful in detecting cellular proliferative disorders, such as by detecting related TGF-beta family members. This utility is asserted in the present specification and supported by the published literature. The specification discloses that GDF-16 is a TGF-beta family member. Based on this fact and the known activities of various TGF-beta family members, a number of utilities were asserted for GDF-16 encoding polynucleotides, vectors, and host cells that are supported by published literature. For example, the specification discloses that GDF-16 can have cell growth and differentiation activity and can be useful as a marker for a cell proliferative disorder (see page 3, lines 2-4; page 4, lines 1-8). The specification also discloses that a GDF-16 polynucleotide, as well as reagents specific for GDF-16 expression, can be useful for diagnosing and treating a cell proliferative disorder (see, page 19, lines 3-10), for example, a malignant cell proliferative disorder (see page 15, lines 17-24). More specifically, the specification discloses that a GDF-16 polynucleotide can be utilized in detecting and diagnosing a cell proliferative disorder by detecting an altered level of expression compared with that of a normal cell (page 19, lines 3-10). Furthermore, the specification discloses that a GDF-16 polynucleotide can be used to detect a close family member of GDF-16 (page 7, lines 18-23).

As indicated above, a number of scientific publications available as of the filing date of the present application, describe specific expression of TGFβ family members, for example the TGFβ-4 (endometrial bleeding associated factor; "ebaf") gene, in cell proliferative disorders, including endometrial bleeding and adenocarcinoma of the colon, ovaries, and testes (see Kothapalli et al. *J. Clin. Invest.* 99, 2342-2350 (May 15, 1997); and Tabibzadeh et al., *Frontiers in Bioscience* 2, a18-25 (July 15, 1997), both of which are of record in this case). As the Examiner noted in Paper No. 17, the polynucleotide sequence of TGFβ-4 (ebaf), disclosed in U.S. Pat. No. 5,916,751 (The '751 Patent), contains a region of 303 nucleotides that is 92% homologous to SEQ ID NO: 1 of the subject application. As such, Applicants submit that one skilled in the art, viewing the subject application, and having knowledge of the Kothapalli et al. and Tabibzadeh et al. references, would appreciate that the polynucleotides of the invention, and expression vectors and host cells which are useful for the production of the polynucleotides, are

useful in the detection of TGFβ family members whose expression is correlated with cell proliferative disorders, such as TGFβ-4 (ebaf). Therefore, the utilities taught in the specification are further supported by the published literature. Accordingly, it is respectfully requested that the rejection of claims 2, 4 to 11, and 53 to 55, under 35 U.S.C. § 112, first paragraph, be reversed, and the rejection withdrawn.

APPENDICES

Appendix A contains a copy of pending claims 1 to 2, 4 to 42, and 53 to 55. Claims 2, 4 to 11, and 53 to 55 are on appeal. Claims 1, and 12 to 42 have been withdrawn. Claims 3, and 43 to 52 have been cancelled.

CONCLUSION

In view of the above remarks, it is respectfully submitted that claims 2, 4 to 11, and 53 to 55 are in condition for allowance. Accordingly, it is respectfully submitted that the decision of the Examiner, rejecting claims 2, 4 to 11, and 53 to 55, under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 101, be reversed, and the rejections withdrawn.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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EXHIBIT A

CLAIMS PENDING ON APPEAL

1. (Withdrawn): Substantially pure growth differentiation factor-16 (GDF-16).

2. (Previously Presented): An isolated polynucleotide sequence encoding the growth differentiation factor-16 (GDF-16) polypeptide as set forth in SEQ ID NO: 2.

3. (Canceled)

4. (Previously Presented): The polynucleotide sequence of claim 2, wherein the polynucleotide is isolated from a mammalian cell.

5. (Previously Presented): The polynucleotide of claim 4, wherein the mammalian cell is selected from the group consisting of mouse, rat, and human cell.

6. (Previously Presented): An expression vector including the polynucleotide of claim 2.

7. (Previously Presented): The vector of claim 6, wherein the vector is a plasmid.

8. (Previously Presented): The vector of claim 6, wherein the vector is a virus.

9. (Previously Presented): A host cell stably transformed with the vector of claim 6.

10. (Previously Presented): The host cell of claim 9, wherein the cell is prokaryotic.

11. (Previously Presented): The host cell of claim 9, wherein the cell is eukaryotic.

12. (Withdrawn): Antibodies that bind to the polypeptide of claim 1 or fragments thereof.

13. (Withdrawn): The antibodies of claim 12, wherein the antibodies are polyclonal

14. (Withdrawn): The antibodies of claim 12, wherein the antibodies are monoclonal.

15. (Withdrawn): A method of detecting a cell proliferative disorder comprising contacting the antibody of claim 12 with a specimen of a subject suspected of having a GDF-16 associated disorder and detecting binding of the antibody.

16. (Withdrawn): The method of claim 15, wherein the detecting is in vivo.

17. (Withdrawn): The method of claim 16, wherein the antibody is detectably labeled.

18. (Withdrawn): The method of claim 17, wherein the detectable label is selected from the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound and a chemiluminescent compound.

19. (Withdrawn): The method of claim 15, wherein the detection is in vitro.

20. (Withdrawn): The method of claim 19, wherein the antibody is detectably labeled.

21. (Withdrawn): The method of claim 20, wherein the label is selected from- the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound, a chemoluminescent compound and an enzyme.

22. (Withdrawn): A method of treating a cell proliferative disorder or immunologic disorder associated with expression of GDF-16, comprising contacting the cells with a reagent which suppresses the GDF-16 activity.

23. (Withdrawn): The method of claim 22, wherein the reagent is an anti-GDF- 16 antibody.

24. (Withdrawn): The method of claim 22, wherein the reagent is a GDF-16 antisense sequence.

25. (Withdrawn): The method of claim 22, wherein the reagent which suppresses GDF-16 activity is introduced to a cell using a vector.

26. (Withdrawn): The method of claim 25, wherein the vector is a colloidal dispersion system.

27. (Withdrawn): The method of claim 26, wherein the colloidal dispersion system is a liposome.

28. (Withdrawn): The method of claim 27, wherein the liposome is essentially target specific.

29. (Withdrawn): The method of claim 28, wherein the liposome is anatomically targeted.

30. (Withdrawn): The method of claim 29, wherein the liposome is mechanistically targeted.

31. (Withdrawn): The method of claim 30, wherein the mechanistic targeting is passive.

32. (Withdrawn): The method of claim 30, wherein the mechanistic targeting is active.

33. (Withdrawn): The method of claim 32, wherein the liposome is actively targeted by coupling with a moiety selected from the group consisting of a sugar, a glycolipid, and a protein.

34. (Withdrawn): The method of claim 33, wherein the protein moiety is an antibody.

35. (Withdrawn): The method of claim 34, wherein the vector is a virus.

36. (Withdrawn): The method of claim 35, wherein the virus is an RNA virus.

37. (Withdrawn): The method of claim 36, wherein the RNA virus is a retrovirus.

38. (Withdrawn): The method of claim 37, wherein the retrovirus is essentially target specific.

39. (Withdrawn): The method of claim 38, wherein a moiety for target specificity is encoded by a polynucleotide inserted into the retroviral genome.

40. (Withdrawn): The method of claim 38, wherein a moiety for target specificity is selected from the group consisting of a sugar, a glycolipid. and a protein.

41. (Withdrawn): The method of claim 40, wherein the protein is an antibody.

42. (Withdrawn): A method for identifying a GDF-16 receptor polypeptide comprising:

a) incubating components comprising GDF- 16 polypeptide and a cell expressing a receptor or a soluble receptor under conditions sufficient to allow the GDF-16 to bind to the receptor;

b) measuring the binding of the GDF-16 polypeptide to the receptor; and

c) isolating the receptor.

43-52 (Canceled).

53. (Previously Presented): An isolated polynucleotide comprising:

a) a nucleotide sequence encoding the growth differentiation factor-16 (GDF-16) polypeptide as set forth in SEQ ID NO: 2;

b) a nucleotide sequence according to SEQ ID NO:1, wherein T can also be U; or

c) a nucleotide sequence complementary to the entire nucleotide sequence of SEQ ID NO:1.

54. (Previously Presented): An expression vector including the polynucleotide of claim 53.

55. (Previously Presented): A host cell stably transformed with the vector of claim 54.